Summary of Safety and Effectiveness Data

I. GENERAL INFORMATION

Device Generic Name:	Mammogram Image Analysis System
Device Trade Name:	Second Look™
Applicant's Name and Address:	CADx Medical Systems, Inc U.S. Agent: Parexel International Corporation 195 West Street Waltham, MA 02451-1163
Date of Panel Recommendation:	Not applicable, see Section XII
Premarket Approval Application (PMA):	P010034
Dates of Good Manufacturing Practice Inspections:	
Qualia Computing, Inc.	August 29, 2001
Colorado MEDtech, Inc.	July 24, 2001
CADx Medical Systems	October 23, 2001
Date of Notice of Approval to Applicant:	January 31, 2002

II. INDICATIONS FOR USE

The Second Look™ computer-aided detection system for mammography is intended to identify and mark regions of interest on standard mammographic views to bring them to the attention of the radiologist after the initial reading has been completed. Thus, the system assists the radiologist in minimizing observational oversights by identifying areas on the original mammogram that may warrant a second review.

III. CONTRAINDICATIONS

There are no contraindications for use of this device.

IV. WARNINGS AND PRECAUTIONS

Warnings and Precautions for use of this device are stated in the attached product labeling. (See Attachment)

V. DEVICE DESCRIPTION

The Second Look™ system consists of the following major components: barcode reader, digitizer, computer (dual processor system), touchscreen monitor, and printer.

The Second Look™ system is a single, self-contained unit that can be used with any mammography illuminator. It was designed to be compact in order to fit into crowded workspaces. (See Figure 1)

Figure 1: Second Look™ System

The operator places mammogram films into the Second Look™ and it in turn creates a printout for the radiologist. After a patient's films are exposed, developed and quality checked, they are ready to be processed. The operator loads the films into the Second Look™'s digitizer receiver tray, enters the patient data on the work list with the keyboard or barcode reader, and issues the required commands using the touchscreen. The digitizer creates a digital representation of the mammogram by scanning it with a laser beam.

Next, Second Look™ uses image processing and pattern recognition algorithms hosted on a personal computer to detect potential areas of concern for further consideration by the radiologist.

Finally, Second Look™ produces a Mammagraph™ (see Figure 2), a paper printout of results that contains identification of patient and technologist, images of the digitized film with any potential areas of concern marked, and a key for the markers. The operator collects these printed images and adds them to the case folder in preparation for the radiologist review.

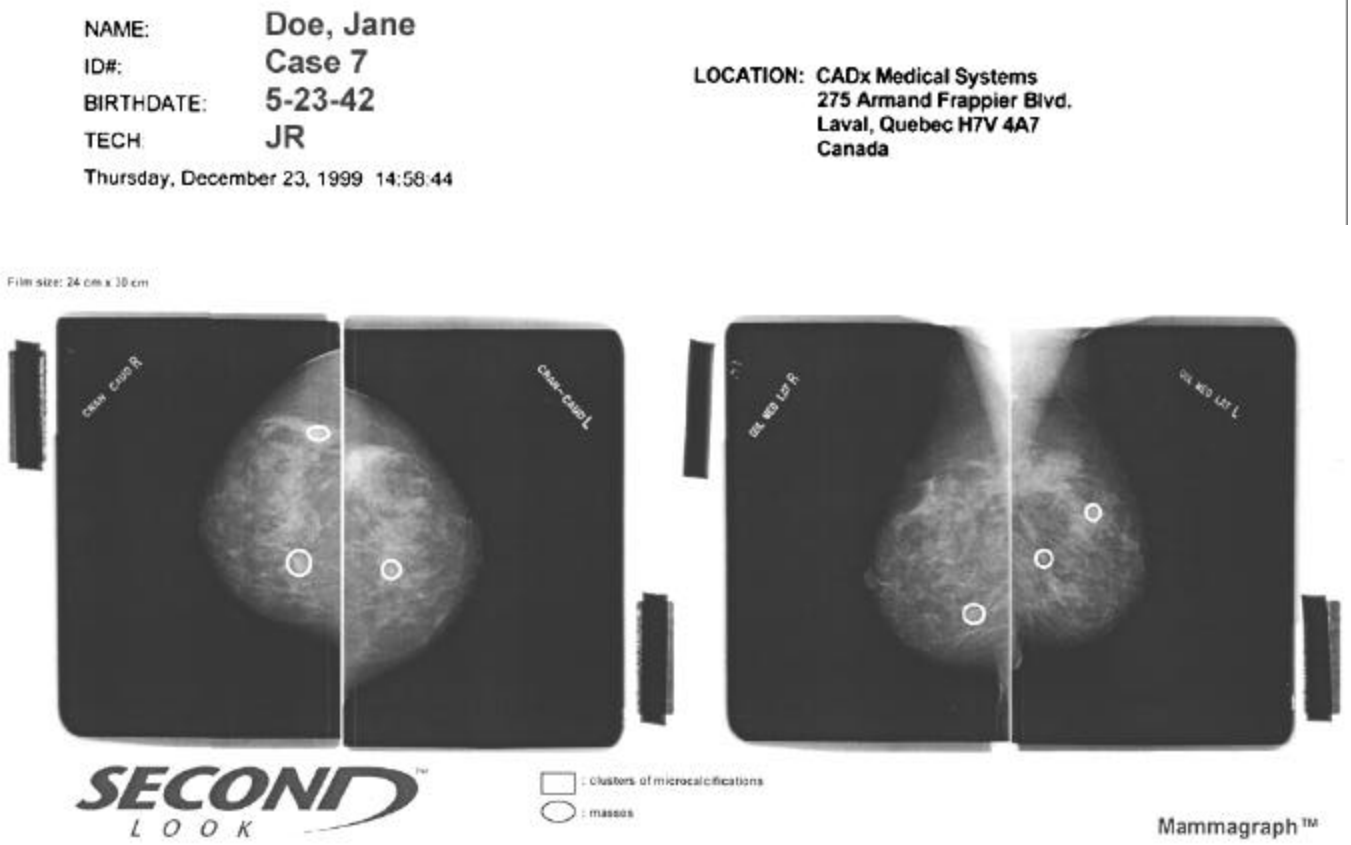

Figure 2**: Second Look™ Output: The Mammagraph**Ô

Areas of concern identified by Second Look™ include potentially suspicious clusters of microcalcifications and masses. Potential clusters of microcalcifications are marked by rectangles (CalcMarks™) and potentially suspicious masses are marked with ellipses (MassMarks™) on the output. Each marker (rectangle or ellipse) is placed at the location of a potential lesion detected by Second Look™ and sized to show the approximate size of the lesion. This printout is used by the radiologist to identify areas of concern on the screening mammograms after the completion of the initial review of the films.

To interpret a case, the radiologist is instructed to review each mammogram in the conventional manner. Then the radiologist should review the Second Look™ Mammagraph™ after determining whether or not

a work-up is indicated from the initial review of the patient mammogram. The radiologist then "looks back" at the original mammograms in those locations corresponding to any marks on the Mammagraph™. If there are no marks made by Second Look™ on the Mammagraph™, then no re-evaluation of the mammogram is necessary. Work-up decisions must not be based on the Mammagraph™, but on review of the mammogram and supporting clinical information.

Second Look™ detects clustered microcalcifications that may be indicative of malignancies. The system filters the image to intensify small mammographically bright spots. These intense regions are then segmented from the background by comparison to local brightness values, and the shape of each potential microcalcification is analyzed. Bright spots typically associated with malignant regions are passed to a clustering stage. The clustering stage forms groups of individual calcifications such that no detection is more than 3 millimeters from another detection in that cluster. Furthermore, each cluster must have more than 3 calcifications. Second Look™ then computes the statistics of the spatial and intensity distributions of the microcalcifications in the clusters. Those clusters satisfying the matching requirements are stored for subsequent input to a post processing stage.

In addition to microcalcifications, Second Look™ also detects suspicious densities. Second Look™ nonlinearly filters a 700-micron resolution version of the digital image such that locally bright and approximately round regions are emphasized. Statistics of the size and approximate shape of these spots in the filtered images are then computed and compared to reference values.

Initial detections from the microcalcification and density detectors of Second Look™ are generated on a per image basis. The inputs to the post processing stage are metrics proportional to the estimated likelihood of malignancy for each detection on all the images from a case. Each detection is then evaluated in the context of all the detections within that case. Classifiers are designed to pass the set of detections most likely to contain a malignancy. Second Look™ is designed to put marks on the Mammagraph™ only on regions that may be indicative of cancer; however, in doing so Second Look™ will mark many non-malignant areas.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

The current procedure for reviewing mammograms involves a radiologist's review of the films on a lightbox or motorized film viewer. Commonly, the radiologist will use a magnifying glass to facilitate the identification of subtle features on the film. Studies have shown that double reading results in a 5-15% gain in sensitivity. Even though clinically effective, double reading is not commonly performed.

VII. MARKETING HISTORY

Second Look™ has been marketed in Europe, Asia/Pacific, Australia and Canada. There have not been any adverse effects reported, nor has the system been withdrawn from any country.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

There are no known direct risks to safety or health caused by, or related to, the use of the device. The indirect risks are that the device will fail to identify and mark some actionable lesions and will mark some actionable lesions that do not require further action. However, the potential for missed lesions is not increased over unaided screening mammography when Second Look™ is used as labeled.

IX. NON-CLINICAL LABORATORY STUDIES

Non-clinical studies were conducted throughout the design and development of the Second Look™ System. These studies were designed to develop and analyze the design of the Second Look™ System.

Assessment of CAD Algorithm Performance- The applicant performed a quantitative assessment of the Second Look™ CAD algorithms based on testing from an in-house library of over one thousand mammograms with known malignancies as well as normal images. The in-house library was collected according to a formal protocol. The results provided demonstrate that the system is able to detect features associated with microcalcifications and masses.

The applicant also performed a quantitative assessment of the Second Look™ internal processing time performance. Results demonstrate that the Second Look™ System processes film within the times specified based on film size.

In addition, a formal focus group and in-depth interviews were conducted to characterize the interactions between hardware and software to develop a user friendly system configuration and graphic user interface.

Software / System Verification and Validation - CADx Medical Systems Inc. and Qualia Computing, Inc. have performed a device hazard analysis from both the patient and user perspective and mitigated identified hazards. They also performed an appropriate verification and validation process. These processes demonstrate that the software and hardware will operate as described in the specifications.

System Reliability - Seven (7) Second Look™ systems were installed at the seven (7) clinical trial sites participating in the prospective study between September 1999 and July 2000. The system downtime, for component replacement, was estimated at 18 days for the 59 months of the system operation at all sites.

Safety / Declaration of Conformance to Standards - Second Look™ complies with the following electrical safety and EMC Standards:

EN 60601-1/95
UL 2601-1, Second Edition
CAN/CSA C22.2 No. 601.1-M90

X. CLINICAL STUDIES

Two comprehensive studies, ROSE-1 and ROSE-2, were conducted to evaluate the use of the Second Look™ system in breast cancer screening.

ROSE-1
The first, ROSE-1, was a multi-institutional study with 3 components: ROSE-1M assessed the reduction in false negatives resulting from the system's detection of missed cancers; ROSE-1D assessed the sensitivity of the system in detecting cancers on mammograms that led to the diagnosis; and ROSE-1R assessed the reproducibility of the system's markings.

ROSE-1M

The ROSE-1M study assessed the number of previously overlooked cancers that might have been detected and worked up by the radiologist had she or he been using Second Look™. Seventeen (17) institutions enrolled 402 screening mammography cases that were originally interpreted as normal or benign within 24 months prior to the screening mammogram that led to cancer diagnosis. Of these 402 cases, 377 had both the current mammogram and the prior mammogram available for analysis. The 377 prior mammograms underwent independent, blinded review by 3 radiologists (the panel) for detection and recommendation of work-up of mammographic abnormalities. At least one of the panel radiologists recommended work-up in 313 cases, with the other 64 cases recommended for work-up by none of them. Of the 313 cases, 177 had one or more work-ups confirmed to be at the locations of subsequently diagnosed cancers by 2 other (truthing) radiologists. The truthing radiologists worked independently of each other but came to consensus over initial disagreements. They worked unblinded, with the help of the subsequent mammogram that led to the diagnosis of cancer.

Of these 177 previously missed cancers, approximately 66% were represented primarily by masses and 34% by microcalcifications. The masses included spiculated and non-spiculated masses, architectural distortions, and asymmetric densities. These 177 mammograms were then processed by Second Look™. The system produced a Mammagraph™ on which MassMarks™ and CalcMarks™ were identified. The locations of these marks were compared to the locations of the subsequently diagnosed cancers. This process measured the sensitivity of the Second Look™ system in detecting missed cancers, but there remained to be determined how many of these would have led the radiologist to recommend work-up.

Since a correct mark by the Second Look™ system in actual clinical practice would only lead to a useful result if the radiologist using it felt that the mark indicated a region that was suspicious enough to warrant further work-up, the number of correct marks needed to be adjusted downward. As a surrogate method of estimating this adjustment, the proportion of blinded panel radiologists who correctly identified the missed cancers was used as a likelihood multiplier. This proportion was either 0/3, 1/3, 2/3, or 3/3. Use of this proportion resulted in a lower bound to the estimated adjustment, for the following reason. The panel radiologists who failed to identify a region could have failed on the basis of either an error of detection or an error of interpretation, but the distribution of cases between these two types of errors was not recorded. So it was simply assumed that all lesions had been detected by all three of the unaided panelists and that failures to recommend work-up were due strictly to errors of interpretation. Then multiplying by 0/3, 1/3, etc. results in the worst-case scenario for actionability of any lesion marked by the system.

By this method it was determined that of these 177 missed cancer cases 62.7% were marked by the Second Look™, and of these at least 80.3 would have been worked-up if they had been pointed out to the clinical radiologist.

Retrospective review of the 313 cases by the truthing radiologists showed that 242 had retrospectively visible lesions in the location of the subsequent cancer and 71 did not. This 242 included 177 cancers that at least one of the three panel radiologists called actionable plus 65 which none of them called actionable. As a conservative estimate, all 64 of the cases not submitted to the truthing radiologists for determination of lesion visibility were arbitrarily assumed to have retrospectively visible lesions. Using this assumption, the maximum number of retrospectively visible false negative cases is 306 (242 + 64). Therefore, the reduction in false negatives with the use of Second Look™ is at least 26.2% (80.3/306). With a 95% confidence interval of 21.9% to 30.7%, this 26.2% minimum reduction in false negatives is clinically significant.

ROSE-1D

The ROSE-1D study examined the sensitivity of Second Look™ in detecting diagnosed cancers on screening mammograms. Seventeen (17) institutions enrolled 930 subjects with screening mammograms that led to the diagnosis of breast cancer (67% of which were represented primarily by masses and 33% by calcifications). The 930 mammograms were processed by Second Look™. The system correctly marked the cancer in 791 of these 930 cases. Thus, Second Look™ had a sensitivity of 85% for screen-detected cancer cases.

ROSE-1R

The ROSE-1R study evaluated the reproducibility of the Second Look™ system. Twenty-five (25) screen-detected cancer cases from the ROSE-1D study were processed 10 times through each of 3 Second Look™ systems. The system correctly marked the lesion in 745 of 750 cases. Therefore, the Second Look™ system reproducibility was over 99%.

ROSE-2

The second pivotal study, ROSE-2, was a multi-institutional prospective study designed to show that the use of the Second Look™ system did not appreciably increase the number of suspicious regions recommended for further work-up by radiologists reading screening mammograms. The work-up rates of radiologists were prospectively determined before and after the use of Second Look™. In addition, the interpreting radiologists estimated the additional time associated with the use of Second Look™ as a percentage of total reading time.

Ten (10) experienced mammographers at 5 institutions prospectively interpreted a total of 3,946 sequential screening mammograms. Each mammogram was then processed by Second Look™, and the same radiologists then re-evaluated the mammogram with the Mammagraph™. Of the 3,946 cases, 657 were recommended for work-up by radiologists before the use of Second Look™. After the use of Second Look™ an additional 20 cases were recommended for work-up, for a total of 677 cases. Therefore, the work-up rate of radiologists was 16.6% (657 of 3,946) before use of Second Look™ and 17.2 % (677 of 3,946) afterward. The 95% confidence intervals for these work-up rates were (15.5% – 17.8%) before Second Look™ use and (16.0% – 18.4%) with it. This demonstrated that the 0.5% (20 of 3,946) increase in work-up rate due to the use of Second Look™ was statistically and clinically insignificant.

In 3,631 of 3,946 prospective cases (92%) the estimated additional reading time to use Second Look™ was 20% or less.

In addition, historical work-up rates for the same radiologists in the months prior to the prospective cases were compared to their rates before the use of Second Look™ in order to illustrate the variability inherent in the process of reading screening mammograms. For this study, work-up included additional mammographic views, short-interval follow-up, ultrasound, other advanced imaging modalities, or recommendation for biopsy. Of the 3,876 historical cases, 516 were worked-up by radiologists without the use of Second Look™ for a 13.3% historical work-up rate. The 95% confidence interval on this work-up rate was (12.3% – 14.4%). Thus, there was no overlap in the confidence intervals between the historical work-up rate and the work-up rate prior to use of Second Look™ compared to the considerable overlap of confidence intervals between the work-up rates before and after Second Look™ use. Consequently, the inherent variability in radiologist work-up rates was larger than the increase due to the use of Second Look™. This adds further evidence that the increase in work-up rate due to the use of Second Look™ is clinically insignificant.

XI. CONCLUSIONS DRAWN FROM STUDIES

- The use of the Second Look™ system on screening mammograms led to a clinically significant reduction in missed cancers (false negatives) of at least 26.2% (95% CI 21.9%, 30.7%).
- The use of the Second Look™ system led to a clinically and statistically insignificant increase in the number of work-ups recommended by radiologists reading screening mammograms from 16.6% (95% CI 15.5%, 17.8%) unaided to 17.2% (95% CI 16.0%, 18.4%) aided.

In summary, Second Look™ aids a radiologist in detecting breast cancer on screening mammograms.

XII. PANEL RECOMMENDATION

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Radiological Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CDRH DECISION

The sponsor's manufacturing and control facilities were inspected on July 24, August 29, and October 23, 2001, and they were found to be in compliance with Good Manufacturing Practice regulations.

Based on the review of the information submitted the PMA (which includes all modules and amendments), the device has been found to be reasonably safe and effective for its intended use when used in accordance with the instructions for use.

FDA issued an approval order on January 31, 2002

XVI. APPROVAL SPECIFICATIONS

Directions for use: See attached labeling.

Hazards to Health from Use of the device: See Indications, Contraindications, Warnings, and Precautions in the attached labeling.

Post Approval Requirements and Restrictions: See attached approval order.